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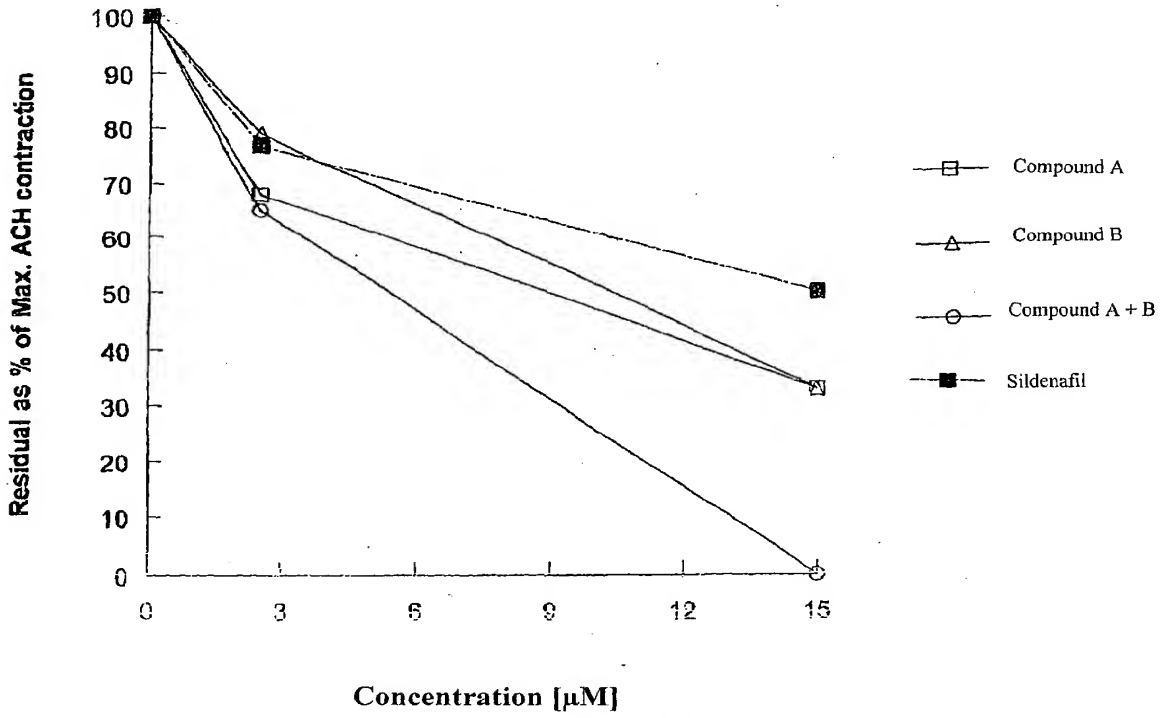
(54) Novel pyrazolopyrimidones and their use as PDE inhibitors

(57) The present invention relates to novel pyrazolopyrimidones, compositions comprising pyrazolopyrimidones as well as to the use of compounds and the composition for the production of a medicament acting as a PDE inhibitor, such as for the treatment of erectile dysfunction.

Figure 1



EP 1 460 077 A1

Description

[0001] The invention relates to novel pyrazolopyrimidones, compositions comprising pyrazolopyrimidones as well as to the use of the pyrazolopyrimidones and the compositions for the preparation of a medicament.

[0002] Substituted pyrazolopyrimidones are known in the prior art, in particular as anti-convulsants, sedatives, and anti-inflammatory and gastric antisecretory agents (US patent No. 3,939,161) and for use in the treatment of cardiovascular disorders (US patent No. 4,666,908).

[0003] Early generation of PDE inhibitors exhibited pharmacological effects on more than one PDE. This is due to vast distribution of PDEs in different organs in the body and the lack of fully understanding the mechanism of such inhibitors. Although PDE inhibitors are claimed to act more selectively on one PDE family, but their pharmacological action is shown to act on more than a single site (organ). This can be attributed to their structure, which is usually a combination of two active parts.

[0004] The treatment of erectile dysfunction is undergoing a tremendous advancement. Three major medicaments as phosphodiesterase inhibitors, namely sildenafil, tadalafil and vardenafil, are commercially available. From these compounds, it is known that they show significant toxicity and side-effects.

[0005] It is an object of the present invention to provide novel compounds or compositions which might be used for the production of a medicament acting as PDE inhibitor, such as for the treatment of erectile dysfunction, which has a sufficient activity and shows decreased toxicity and side-effects as the presently known medicaments.

[0006] This object is achieved by the novel compounds as disclosed in claim 1, the compositions as disclosed in claim 3 as well as the uses of claims 8 and 9.

[0007] Further preferred embodiments are disclosed in the sub-claims. Compound B is disclosed in EP 1219 614 A1.

[0008] Surprisingly, it was found that the action of compounds and composition of the present invention on tissues containing PDE are higher compared to compounds known in the prior art. Especially, the inventive compositions show a synergistic action on tissues containing PDEs, the action being higher than either one molecular entity or if both parts are jointly together in one compound.

[0009] Surprisingly, it was also found that compounds and compositions of the present invention are especially active for the treatment of erectile dysfunction with a strongly improved efficiency. Experiments have shown that those compounds and compositions are at least as active and more favorable as to toxicity and side-effects as the presently most widely used medicament for the treatment of erectile dysfunction, namely sildenafil (Viagra®).

[0010] Presently, best results are obtained, for compositions with a compound (A) wherein R_1 and R_2 are both hydrogen, R_3 is methyl and R_4 is n-propyl. Also, it is preferred for the compound (B) of the composition that X is N, R_0 is H, methyl, methoxy or ethoxy.

[0011] The surprising effect achieved by the present invention is now further illustrated in the examples section with reference to the accompanying drawing (Figure 1) which shows for a single compound A, a single compound B, a mixture of compounds A and B and sildenafil the dependency of residual of maximum ACH contraction (%) on the concentration of the compounds. Compound A used has the structure of formula (XI), wherein R_1 and R_2 are both hydrogen, R_3 is methyl and R_4 is n-propyl. As can be clearly seen from the figure, the mixture of both compounds A and B shows superior activity than for each compound alone and even superior activity than for sildenafil.

[0012] Further, the effect of administration of above compounds and compositions was studied by administrating them to both rats and rabbits.

[0013] The purpose of the study was to compare the biological activity of the compounds and compositions of the present invention with that of sildenafil. In particular, the erection episodes and penile erection indexes of the compounds and compositions in the treatment of male rats and rabbits were determined.

[0014] The Penile Erection Index (PEI) is calculated or expressed as the % of rats or rabbits exhibiting at least one episode of penile erection multiplied by the number of total episodes, within a time period of 2 hours. Details on the determination of PEI values can be found in e.g. H.H. Ang and M.K. Sim, Effects of Eurycoma longifilia Jack on Penile Erection Indes and Homosexual Mounting in Rats, Pharmaceutical Sciences, 3 (1997), 117-19; and A. Benassi-Benelli, F. Ferrari and B. Pellegrini Quaratotti, Penile erection Induced by Apomorphine and N-n-propyl-norapomorphine in Rats, Arch. Int. Pharmacodyn 242 (1979), 241-247. The episode is a description for rat sucking their penus.

[0015] Rabbit experiments where performed according to E. Bischof and K. Schneider, "Intemational Journal of Impotence Research", 13 (2001) 230 - 235, and rat experiments where performed according to EP 1057829 A1.

[0016] Studying the penile erection index for rabbits in dependency on time yields the results given in table 1 for sildenafil and the inventive compound (XI).

Table 1

Time (min)	Sildenafil	Compound XI
0	0	0
5	18.318	12.8
10	16.694	9.5
15	15.22	7.4
20	13.108	5
30	11.218	1.8
40	7.364	1.8
50	2.94	1

[0017] The data of table 1 show that sildenafil has greater efficacy than compound XI. However, the surprising effect is that using compound XI or a composition as disclosed in the present invention leads to almost similar effect as that of sildenafil, but at optimum concentration and mixing ratios the side effect of the medicament based on the compounds and compositions of the present invention is less than for sildenafil. Of course, the ratio will be dependent on the target medication, for example erectile dysfunction or asthma treatment, etc..

[0018] Further, the effect on penile length of rats was studied and the following results are given in table 2 for a compound of the present invention and in table 3 for sildenafil. The penile length is indicative of the efficacy of the administered medicament.

Table 2

Compound XI			
dose mg/kg	No. of rats	No. of episodes	PEI
Vehicle	10	0	0
2	10	7	280
5	10	13	910
10	10	8	400
20	10	9	270

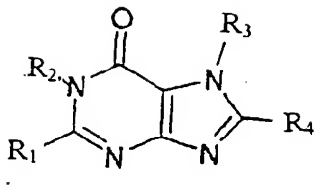
Table 3

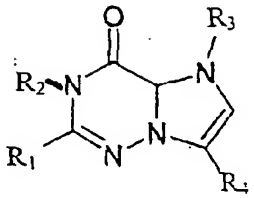
Sildenafil			
dose mg/kg	No. of rats	No. of episodes	PEI
Vehicle	10	0	0
0.0781	10	3	90
0.1562	10	5	150
0.3125	10	7	350
0.6250	10	14	980

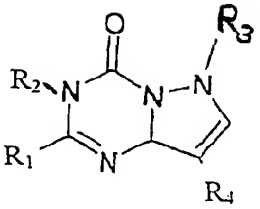
[0019] Features disclosed in the description, in the claims and in the drawing may, both separately and in any combination thereof, be material for realizing the invention in diverse forms thereof.

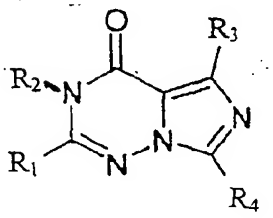
Claims

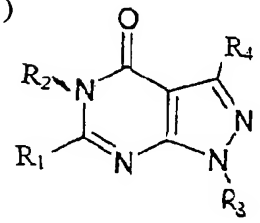
1. Compound, represented by one of the structural formulas:

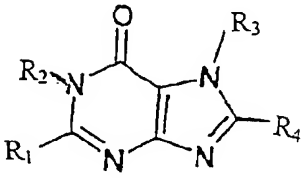
(I) 

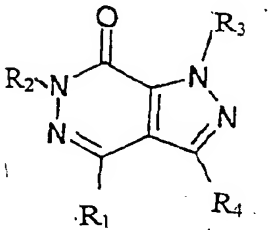
(II) 

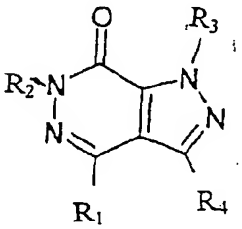
(III) 

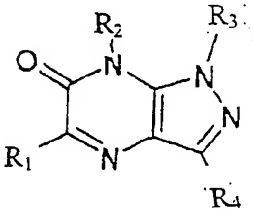
(IV) 

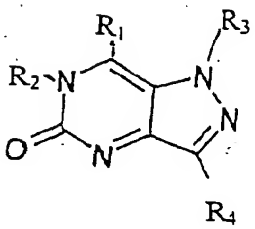
(V) 

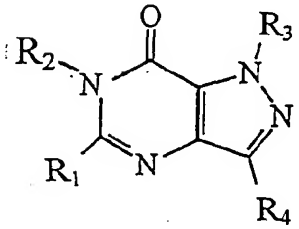
(VI) 

(VII) 

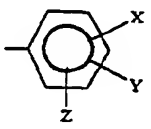
(VIII) 

(IX) 

(X) 

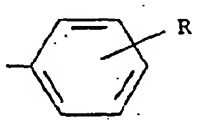
(XI) 

or mixtures thereof wherein R_1, R_2, R_3, and R_4 are independently hydrogen, halogen, hydroxyl, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, haloalkyl, alkylaryl, aryl, aralkyl, alkoxy, carboxy or heterocyclyl, all of these substituents being substituted or unsubstituted, with the exception of formula (XI), wherein R_1 being hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, piperidinomethyl, methoxymethyl, N-methylpiperazino methyl, carbethoxy, p-chlorophenoxymethyl or Ar-(CH_2)n-, wherein n is 0-4; and Ar is



or 2, 3, or 4-pyridyl, wherein X, Y, and Z are independently (1) hydrogen; (2) lower alkyl of from one to six carbons, inclusive; (3) halogen; (4) hydroxyl; (5) lower alkoxy of from one to six carbons, inclusive; (6) nitro; (7) amino; (8)

NR'R" wherein R' and R" are each independently (a) hydrogen or (b) lower alkyl of from one to six carbons, inclusive, optionally substituted by (i) amino, (ii) morpholino or (iii) cycloalkyl of from five to seven carbons, inclusive; (9) sulfo; or (10) —SO_2NR'R" wherein R' and R" are as defined above with the proviso that not all of X, Y, and Z can be nitro, amino, or NR'R" at once; and R_2 being hydrogen, C_1-C_4 alkyl, phenyl or

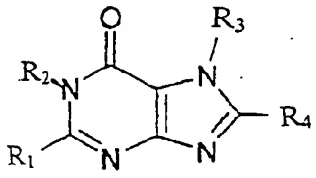


wherein R is a substituent of the group consisting of halo, methyl, trifluoromethyl and di(C_1-C_4)alkylamino (C_1-C_4) alkyloxy; when R_3 and R_4 are both methyl, and pharmaceutically acceptable salts thereof.

2. Compound according to claim 1, wherein R_1 and R_2 are both hydrogen, R_3 is methyl and R_4 is n-propyl.

3. Composition comprising a mixture of compound (A) represented by one of the structural formulas:

(I)



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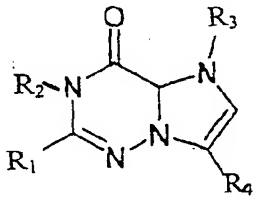

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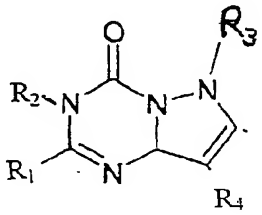

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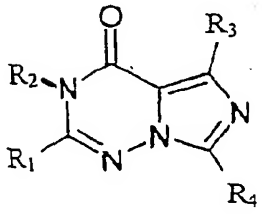

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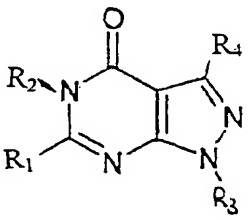

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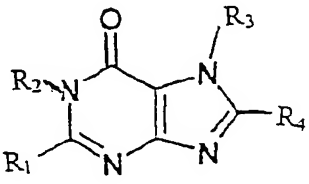

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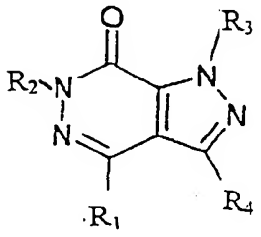

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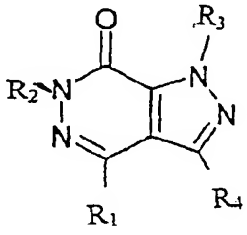

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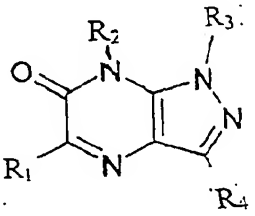

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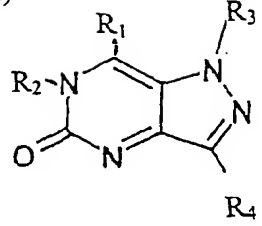

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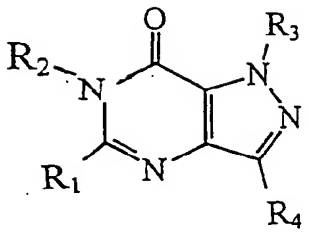
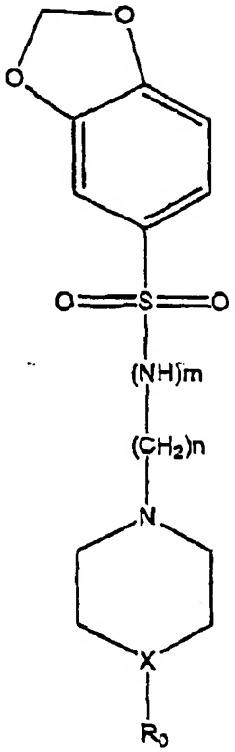


and of compound (B) represented by the structural formula:



wherein

X is chosen from N and C;

R_0 is chosen from H, a lower alkyl group having 1 to 6 carbon atoms, a lower O-alkyl group having 1 to 6 carbon atoms, a lower aldehyde group having 1 to 6 carbon atoms, a benzyl group, a phenyl group, a phenyl group substituted with halogen or O-alkyl having 1 to 6 carbon atoms, a heterocyclic amine group having 3 to 6 carbon atoms, a cycloalkyl group having from 3 to 6 carbon atoms, a cycloalkyl group having from 3 to 6 carbon atoms substituted with O-alkyl having 1 to 6 carbon atoms, and a furyl group;

n is 0, 1, 2, 3 or 4;

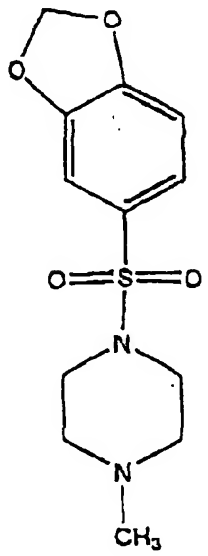
m is 0 or 1;

and pharmaceutically acceptable salts thereof.

4. Composition according to claim 3, wherein X is N.

5. Composition according to claim 3 or 4, wherein R_0 is chosen from H, methyl, methoxy and ethoxy.

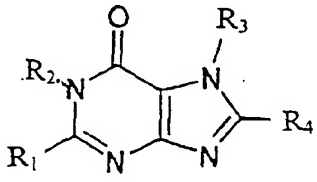
6. Composition according to any of the preceding claims 3 to 5, wherein the compound (B) is:



7. Composition according to any of the preceding claims 3 to 6 further comprising pharmaceutically acceptable adjuvant, diluent, excipient or carrier.

8. Use of a compound represented by the structural formulas:

(I)



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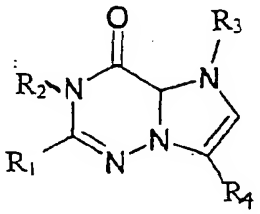

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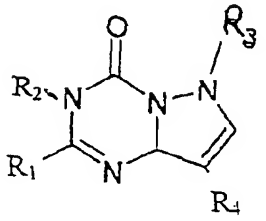

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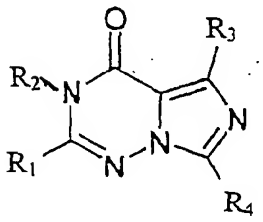

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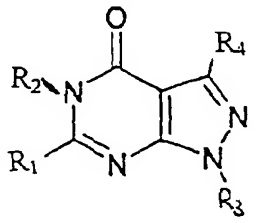

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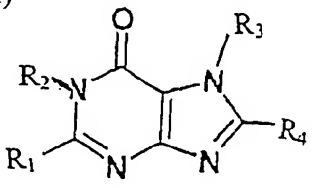
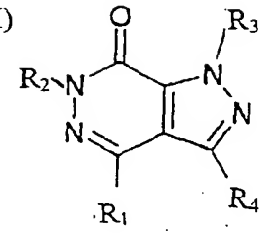
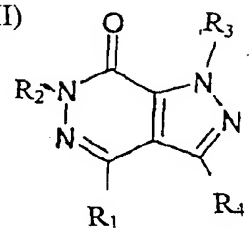
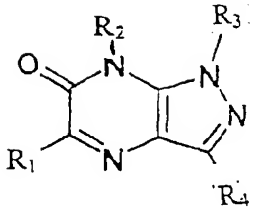
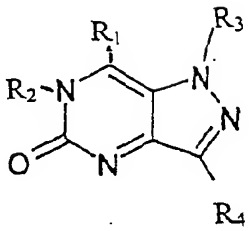
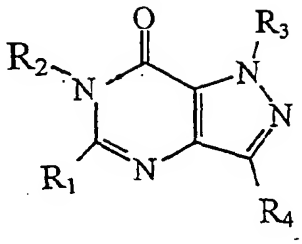


(VII) 

(VIII) 

(IX) 

(X) 

(XI) 

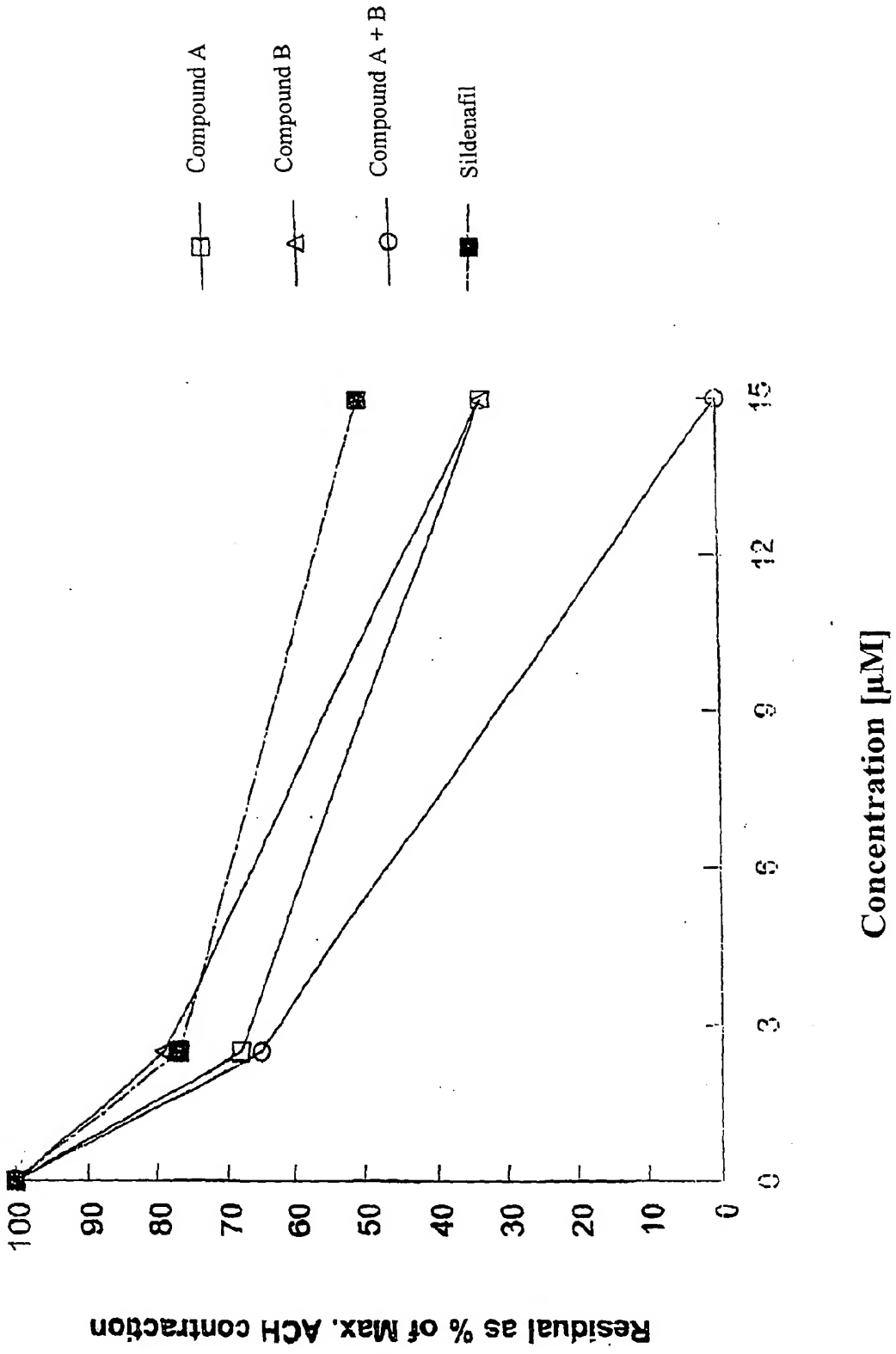
for the production of a medicament acting as a PDE-inhibitor.

9. Use according to claim 8 for the preparation of a medicament for the treatment of erectile dysfunction.

10. Use of a composition according to claims 3 to 7 for the production of a medicament acting as a PDE-inhibitor.

11. Use according to claim 10 for the preparation of a medicament for the treatment of erectile dysfunction.

Figure 1


Compound A
Compound B
Compound A + B
Sildenafil
Residual as % of Max. ACH contraction
100
90
80
70
60
50
40
30
20
10
0
0
3
6
9
12
15
Concentration [µM]

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 04 00 6048

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
D,X	US 3 939 161 A (RATAJCZYK JAMES DANIEL ET AL) 17 February 1976 (1976-02-17) * examples 1-4,6,7,9,11,13-19,23,24,28,29 * -----	1	C07D487/04 A61K31/519 A61P15/10 C07D473/30 A61K31/496
X	EP 1 022 026 A (PFIZER LTD ; PFIZER RES & DEV (IE)) 26 July 2000 (2000-07-26) claims 1, 39 (lines 15-16) and 83 -----	1,8,9	
X	TERRETT N K ET AL: "Sildenafil (VIAGRA<TM>), a potent and selective inhibitor of type 5 CGMP phosphodiesterase with utility for the treatment of male erectile dysfunction" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 6, no. 15, 6 August 1996 (1996-08-06), pages 1819-1824, XP004135609 ISSN: 0960-894X abstract and figure 1, compound II -----	1,8,9	
	-/--		

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

C07D
A61K
A61P

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
The Hague	27 May 2004	Alfaro Faus, I

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

INCOMPLETE SEARCH SHEET C

Application Number
EP 04 00 6048

Claim(s) searched incompletely:
1-11

Claim(s) not searched:
-

Reason for the limitation of the search:

Present claims 1-11 relate to an extremely large number of possible compounds and compositions. Support within the meaning of Article 84 EPC and/or disclosure within the meaning of Article 83 EPC is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula XI and the compositions of compounds of formula XI with compound B as disclosed on pages 3 and 4.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 04 00 6048

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
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EPO FORM 1503 03.82 (P04C10)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 04 00 6048

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82